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(54) Title: INTEGRIN RECEPTOR ANTAGONISTS			
(57) Abstract <p>This invention relates to the seven membered at least one nitrogen containing tricyclic heterocyclic pharmaceutically active compounds which bind to integrins, such as the vitronectin receptor and fibrinogen receptor. Such compounds are useful for inhibiting platelet aggregation and osteoclast attachment to bone.</p>			

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**TITLE**

Integrin Receptor Antagonists

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**FIELD OF THE INVENTION**

This invention relates to pharmaceutically active compounds which bind to integrins, such as the vitronectin receptor and fibrinogen receptor. Such compounds are useful for inhibiting platelet aggregation and osteoclast attachment to bone.

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**BACKGROUND OF THE INVENTION**

Integrins are a family of heterodimeric proteins which generally mediate cell adhesion. Typical of such proteins are the vitronectin receptor (an  $\alpha_v\beta_3$  heterodimer) and the fibrinogen receptor (an  $\alpha_{IIb}\beta_3$  heterodimer). The natural ligands of these receptors (e.g., vitronectin and fibrinogen) have been found to share a common -Arg-Gly-Asp- amino acid sequence, which appears to be critical for binding. In fact, many of the integrin receptors appear to cross react with ligands which possess such an amino acid sequence. For instance, the  $\alpha_{IIb}\beta_3$  receptor reacts with fibronectin and vitronectin, thrombospondin and von Willebrand factor, as well as fibrinogen. Functionally fibrinogen, a dimer having two binding sites for  $\alpha_{IIb}\beta_3$ , reacts with activated receptors found on the surface of platelets. The binding of  $\alpha_{IIb}\beta_3$  receptors on adjacent platelets, by fibrinogen leads to crosslinking and is considered to be a major factor in platelet aggregation. Compounds which inhibit the binding of the  $\alpha_{IIb}\beta_3$  receptor to fibrinogen have been shown to inhibit the

platelet aggregation *in vitro*, and thrombus formation *in vivo*. See, for instance, EP-A 0 341 915.

The vitronectin receptor is found on a variety of cell types, such as on osteoclasts and the endothelial cells lining blood vessels. Recent studies have indicated that the attachment of osteoclasts to the bone matrix is mediated through these cell surface adhesion receptors. For instance, Davies, *et al.*, *J. Cell Biol.*, 1989, 109, 1817, disclose that the osteoclast functional antigen, which is implicated in the regulation of bone resorption, is biochemically related to the vitronectin receptor.

The vitronectin receptor is known to bind to bone matrix proteins, such as

osteopontin, bone sialoprotein and thrombospondin, which contain the tri-peptide Arg-Gly-Asp (or RGD) motif. Thus, Horton, *et al.*, *Exp. Cell Res.* 1991, 195, 368, disclose that RGD-containing peptides and an anti-vitronectin receptor antibody (23C6) inhibit dentine resorption and cell spreading by osteoclasts. Bertolini *et al.*, *J. Bone Min. Res.*, 6, Sup. 1, S146, 252 have shown that cyclo-S,S-N<sup>α</sup>-acetyl-cysteinyl-N<sup>α</sup>-methyl-argininyl-glycyl-aspartyl-penicillamine amide inhibits osteoclast attachment to bone. In addition, Sato, *et al.*, *J. Cell Biol.* 1990, 111, 1713 disclose that echistatin, a snake venom peptide which contains the RGD sequence, is a potent inhibitor of bone resorption in tissue culture, and inhibits attachment of osteoclasts to bone. Fisher, *et al.*, *Endocrinology* 1993, 132, 1411, has further shown that echistatin inhibits bone resorption *in vivo* in the rat. EP 528 587 and 528 586 report substituted phenyl derivatives which inhibit osteoclast mediated bone resorption.

Bondinell, *et al.*, in WO 93/00095 (PCT/US92/05463) and WO 94/14776 (PCT/US93/12436) disclose that certain compounds which have a substituted 6-7 bicyclic ring system are useful for inhibiting the fibrinogen ( $\alpha_{IIb}\beta_3$ ) receptor. Other 6-7 bicyclic ring systems which inhibit the fibrinogen receptor are disclosed by Blackburn *et al.* in WO 93/08174 (PCT/US92/08788). Blackburn *et al.*, WO 95/04057 (PCT/US94/07989) also disclose compounds which have a five- or six-membered ring fused to such 6-7 bicyclic ring to form a tricyclic ring system, which are useful as antagonists of the fibrinogen receptor. Other compounds having 6-7 bicyclic ring systems that selectively inhibit the vitronectin receptor are disclosed in WO 96/00730 (PCT/US95/08306) and WO 96/00574 (PCT/US95/08146). It has now been discovered that certain new tricyclic ring systems are useful templates for preparing integrin receptor antagonists. It has also been discovered that such a ring system may be used as a template, which may be suitably substituted to prepare compounds which are selective for either the fibrinogen receptor or the vitronectin receptor.

## SUMMARY OF THE INVENTION

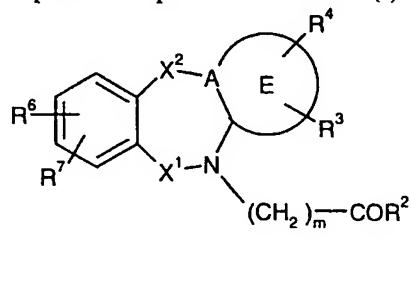
It is an object of this invention to provide compounds of the formula (I), as described hereinafter, which have pharmacological activity for the inhibition of integrin receptors. It is an object of this invention to provide a template which may be suitably substituted to provide selective binding for specific integrin receptors, especially the fibrinogen ( $\alpha_{IIb}\beta_3$ ) or the vitronectin ( $\alpha_v\beta_3$ ) receptor relative to each other and other integrin receptors.

This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically carrier.

This invention is also a method of treating diseases in which the pathology may be modified by binding to an integrin receptor, especially the vitronectin or the fibrinogen receptor. In a particular aspect, the compounds of this invention are useful for treating osteoporosis, atherosclerosis, restenosis, cancer and conditions in which it is desirable to inhibit platelet aggregation, such as stroke, transient ischemia attacks, myocardial infarction and rethrombosis following thrombolytic therapy.

## DETAILED DESCRIPTION

This invention comprises compounds of formula (I):



20

wherein:

- A is C or N;
- E is a five- or six-membered heteroaromatic or heterocyclic ring, or a six-membered aromatic ring;
- X<sup>1</sup> is CHR<sup>1</sup>, C(O) or C(S);
- X<sup>2</sup> is CR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>, S(O)<sub>u</sub> or O;
- R<sup>1</sup> is H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;
- R<sup>2</sup> is -OR', -NR'R'', -NR'SO<sub>2</sub>R'', -NR'OR', -OCR'<sub>2</sub>C(O)OR', -OCR'<sub>2</sub>OC(O)-R', -OCR'<sub>2</sub>C(O)NR'<sub>2</sub>, CF<sub>3</sub> or -COCR'<sub>2</sub>R<sup>2</sup>;
- R<sup>2</sup>' is -OR', -CN, -S(O)<sub>u</sub>R', S(O)<sub>2</sub>NR'<sub>2</sub>, -C(O)R'C(O)NR'<sub>2</sub> or -CO<sub>2</sub>R';
- R' is H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;

R'' is R', -C(O)R' or -C(O)OR<sup>5</sup>;

R''' is C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;

R<sup>5</sup> and R<sup>5'</sup> are independently H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;

5 R<sup>6</sup> is W-(CR'2)<sub>q</sub>-Z-(CR'R<sup>10</sup>)<sub>r</sub>-U-(CR'2)<sub>s</sub>-V- or W'-(CR'2)<sub>q</sub>-U-(CR'2)<sub>s</sub>-;

R<sup>3</sup>, R<sup>4</sup> and R<sup>7</sup> are independently H, halo, -OR<sup>12</sup>, -SR<sup>12</sup>, -CN, -NR'R<sup>12</sup>,

-NO<sub>2</sub>, -CF<sub>3</sub>, CF<sub>3</sub>S(O)<sub>r</sub>-, -CO<sub>2</sub>R', -CONR'2, R<sup>14</sup>-C<sub>0-6</sub>alkyl-, R<sup>14</sup>-C<sub>1-6</sub>oxoalkyl-,

R<sup>14</sup>-C<sub>2-6</sub>alkenyl-, R<sup>14</sup>-C<sub>2-6</sub>alkynyl-, R<sup>14</sup>-C<sub>0-6</sub>alkyloxy-, R<sup>14</sup>-C<sub>0-6</sub>alkylamino- or

R<sup>14</sup>-C<sub>0-6</sub>alkyl-S(O)<sub>r</sub>;

10 R<sup>8</sup> is R', C(O)R', CN, NO<sub>2</sub>, SO<sub>2</sub>R' or C(O)OR<sup>5</sup>;

R<sup>9</sup> is R', -CF<sub>3</sub>, -SR', or -OR';

R<sup>10</sup> is H, C<sub>1-4</sub>alkyl or -NR'R";

R<sup>12</sup> is R', -C(O)R', -C(O)NR'2, -C(O)OR<sup>5</sup>, -S(O)<sub>m</sub>R' or S(O)<sub>2</sub>NR'2;

R<sup>14</sup> is H, C<sub>3-6</sub>cycloalkyl, Het or Ar;

15 R<sup>15</sup> is H, C<sub>1-10</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-8</sub>alkyl or Ar-C<sub>0-8</sub>alkyl;

U and V are absent or CO, CR'2, C(=CR'<sup>15</sup>)<sub>2</sub>, S(O)<sub>n</sub>, O, NR<sup>15</sup>, CR<sup>15</sup>'OR<sup>15</sup>,

CR'(OR")CR'2, CR'2CR'(OR"), C(O)CR'2, CR<sup>15</sup>'<sub>2</sub>C(O), CONR<sup>15</sup>, NR<sup>15</sup>CO, OC(O),

C(O)O, C(S)O, OC(S), C(S)NR<sup>15</sup>, NR<sup>15</sup>C(S), SO<sub>2</sub>NR<sup>15</sup>, NR<sup>15</sup>SO<sub>2</sub>, N=N, NR<sup>15</sup>NR<sup>15</sup>,

NR<sup>15</sup>CR<sup>15</sup>'<sub>2</sub>, NR<sup>15</sup>CR<sup>15</sup>'<sub>2</sub>, CR<sup>15</sup>'<sub>2</sub>O, OCR<sup>15</sup>'<sub>2</sub>, C≡C, CR<sup>15</sup>=CR<sup>15</sup>, Het, or Ar, provided

20 that U and V are not simultaneously absent;

W is R'R"N-, R'R"NRN-, R'R"NRNCO-, R'2NRNC(=NR')-,

R'ONR'C(=NR')-, R<sup>9</sup>-N(R<sub>2</sub>N)-, R<sup>9</sup>-N(R<sub>2</sub>N)-, R<sup>9</sup>-NR"-NR'-, R"R'N(R')-

R"R'N(R')-

NR'-X-, R"R'N(R')-

NR'- or (N);

W' is

25 Q is NR', O or S;

R<sup>a</sup> is H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl,

halogen, OR<sup>1</sup>, SR<sup>1</sup>, COR<sup>1</sup>, OH, NO<sub>2</sub>, N(R<sup>1</sup>)<sub>2</sub>, CO(NR<sup>1</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>;

$R^b$  and  $R^c$  are independently selected from H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl, halogen, OR<sup>1</sup>, SR<sup>1</sup>, COR<sup>1</sup>, OH, NO<sub>2</sub>, N(R<sup>1</sup>)<sub>2</sub>, CO(NR<sup>1</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, or R<sub>b</sub> and R<sub>c</sub> are joined together to form a five or six membered aromatic or non-aromatic ring, optionally substituted by halogen,

5 C<sub>1-4</sub>alkyl, OR<sup>1</sup>, SR<sup>1</sup>, COR<sup>1</sup>, OH, NO<sub>2</sub>, N(R<sup>1</sup>)<sub>2</sub>, CO(NR<sup>1</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, CN, or R"RN(C=NR')-;

X is N=CR', C(O) or O;

Y is absent, S or O;

Z is (CH<sub>2</sub>)<sub>t</sub>, Het, Ar or C<sub>3-7</sub>cycloalkyl;

10 m is 1 or 2;

n is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

r is 0, 1 or 2;

s is 0, 1 or 2;

15 t is 0, 1 or 2;

u is 0, 1 or 2;

v is 0, 1 or 2; and

w is 0 or 1; or

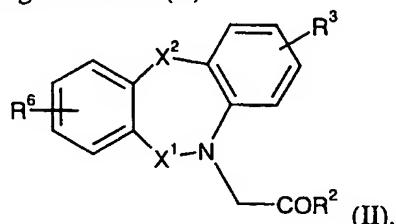
a pharmaceutically acceptable salt thereof.

20 Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each

25 unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as

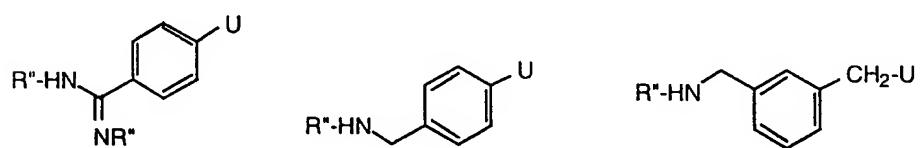
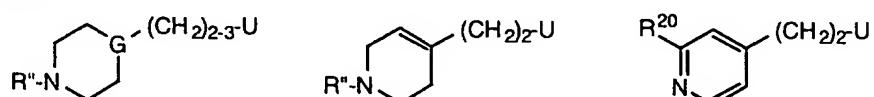
keto-enol tautomers, such as  and , and tautomers of guanidine-type groups, such as R"R'N NR'-X- and R"R'N N-X-, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with R'. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

In one embodiment, this invention is a carbocyclic formula (I) compound according to formula (II):



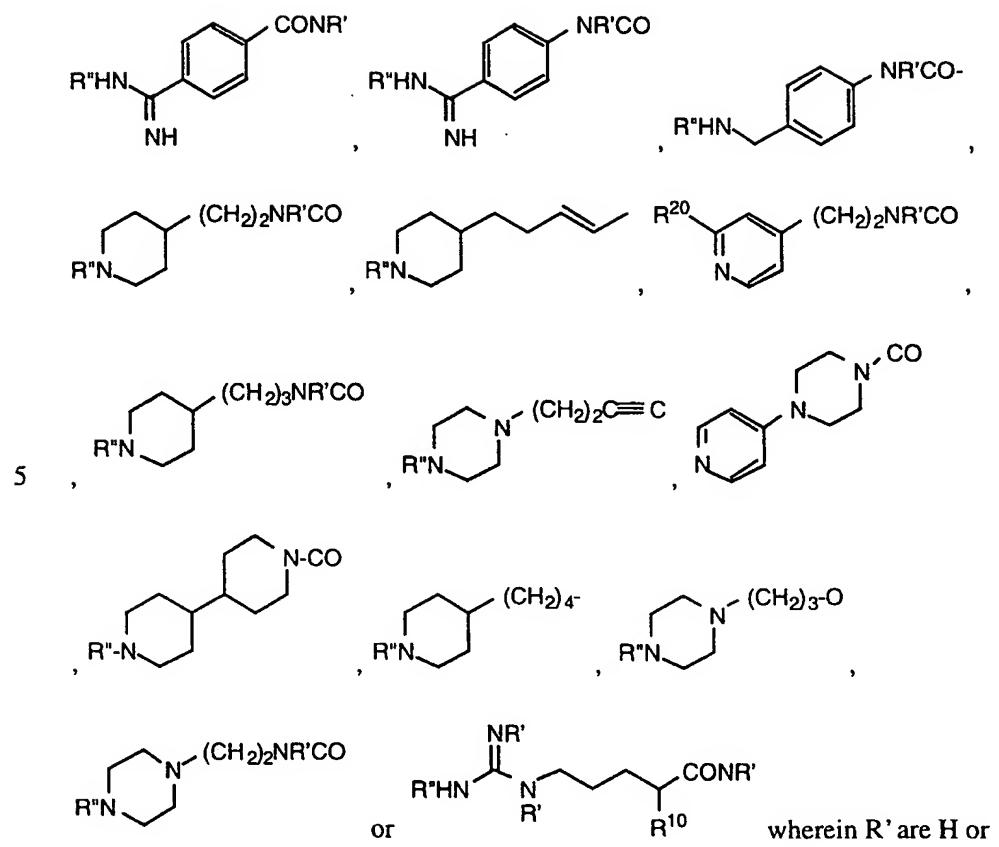
With regards to formula (I):

- 5      Suitably, A<sub>1</sub> is C.
- Preferably, X<sup>1</sup> is CH<sub>2</sub> and X<sup>2</sup> is O.
- Suitably, R<sup>2</sup> is -OH. Suitably, R<sup>3</sup> and R<sup>4</sup> are H.
- Suitably, U is CONR<sup>15</sup>, NR<sup>15</sup>CO, CH<sub>2</sub>CH<sub>2</sub>, or CH<sub>2</sub>O, where R<sup>15</sup> is C<sub>1-10</sub>alkyl, optionally substituted by NO<sub>2</sub>, CN, CO<sub>2</sub>R', R<sup>14</sup>-C<sub>0-6</sub>alkyl or R<sup>14</sup>-C<sub>0-6</sub>alkylamino.
- 10     Suitably, when U is Ar, it is a phenyl ring, preferably 1,3 disubstituted.
- Suitably R<sup>15</sup> is R'. More suitably R<sup>15</sup> is C<sub>1-6</sub>alkyl, most suitably H or methyl.
- Suitable substituents for R<sup>6</sup> when fibrinogen antagonist acitivity is desired
- 15     are:



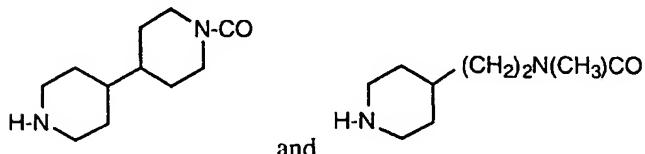
- 20     , R''HNC(=NH)NH-(CH<sub>2</sub>)<sub>3</sub>(CHR<sup>10</sup>)-U, and R''HN-(CH<sub>2</sub>)<sub>5</sub>-U  
wherein G is N or CH, R<sup>20</sup> is hydrogen, amino, mono or di-C<sub>1-4</sub>alkylamino, hydroxy or C<sub>1-4</sub>alkyl, and U is NR'CO, CONR', (CH<sub>2</sub>)CO, CH=CH, ≡C, CH<sub>2</sub>O, OCH<sub>2</sub> and (CH<sub>2</sub>)<sub>2</sub>.

- 25     Particularly good substituents for promoting selective fibrinogen antagonist activity are:

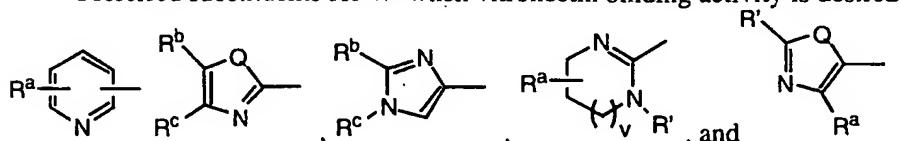


10 C<sub>1-4</sub>alkyl. Preferably R' is methyl and R" is H.

Particularly preferred of such groups for R<sup>6</sup> are:



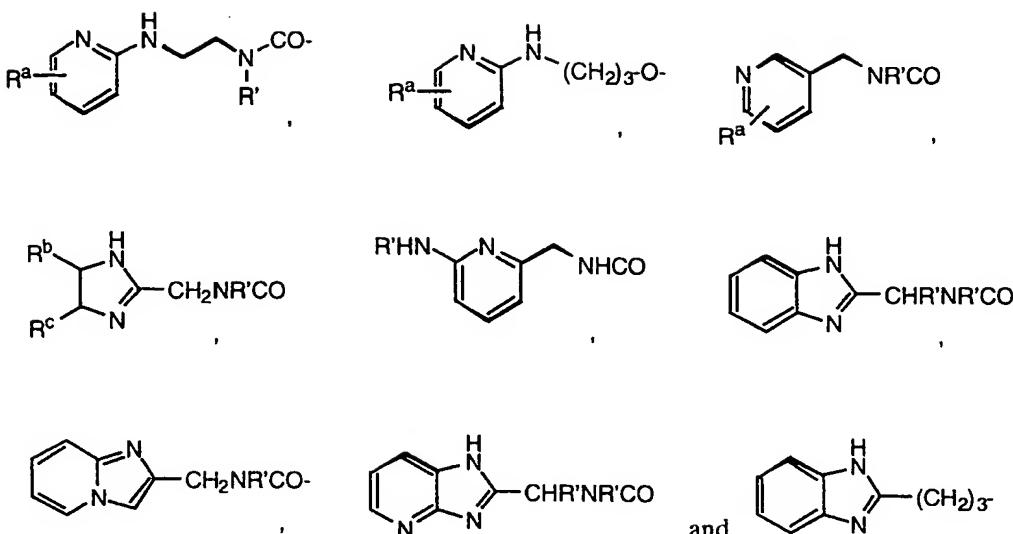
Preferred substituents for W' when vitronectin binding activity is desired are:



15 wherein Q is NH. Preferably, R<sup>b</sup> and R<sup>c</sup> are joined to form a cyclohexyl, phenyl or pyridyl ring. Suitably, R<sup>a</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, halogen or R'NH.

Suitably,  $-(CR'_2)_q-U-$  is  $(CH_2)_q-NR'CO$ ,  $(CH_2)_q-CH_2O$  or  $(CH_2)_q-CH_2CH_2$ .

Specific preferred R<sup>6</sup> substituents for enhancing vitronectin activity are



By appropriate selection of the spacing of the substituent W and/or W' from the phenyl ring of the 6-7 ring system, compounds having selective activity for either the vitronectin and fibrinogen receptor, or dual activity for both receptors,

5 may be obtained. In general, fibrinogen antagonist activity will be favored by an intramolecular distance of about 16 angstroms between the oxygen of the carbonyl moiety attached to the seven-membered ring, and the basic nitrogen moiety of W or W'; while vitronectin antagonist activity will be favored by about 14 angstroms between the respective acidic and basic centers.

10 A specific compound of this invention is 3-[3-(2-pyridyl)aminopropoxy]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-10-acetic acid or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin ( $\alpha_v\beta_3$ ) receptor. Inhibition of the 15 vitronectin receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis and osteoarthritis. Additionally, since the compounds of the instant invention inhibit vitronectin receptors on a number of different types of cells, said compounds would be useful in the treatment of inflammatory disorders, such as 20 rheumatoid arthritis and psoriasis, and cardiovascular diseases, such as atherosclerosis and restenosis. The compounds of Formula (I) of the present invention may be useful for the treatment or prevention of other diseases including, but not limited to, thromboembolic disorders, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplant rejection, septic shock, 25 eczema, contact dermatitis, inflammatory bowel disease, and other autoimmune

diseases. The compounds of the present invention may also be useful for wound healing.

In particular, the compounds of the present invention are useful for the treatment, including prevention, of angiogenic disorders. The term "angiogenic disorders" as used herein includes conditions involving abnormal neovascularization. Where the growth of new blood vessels is the cause of, or contributes to, the pathology associated with a disease, inhibition of angiogenesis will reduce the deleterious effects of the disease. An example of such a disease target is diabetic retinopathy. Where the growth of new blood vessels is required to support growth of a deleterious tissue, inhibition of angiogenesis will reduce the blood supply to the tissue and thereby contribute to reduction in tissue mass based on blood supply requirements. Examples include growth of tumors where neovascularization is a continual requirement in order that the tumor grow and the establishment of solid tumor metastases. Thus, the compounds of the present invention inhibit tumor tissue angiogenesis, thereby preventing tumor metastasis and tumor growth.

Thus, according to the methods of the present invention, the inhibition of angiogenesis using the compounds of the present invention can ameliorate the symptoms of the disease, and, in some cases, can cure the disease.

A preferred therapeutic target for the compounds of the instant invention are eye diseases characterized by neovascularization. Such eye diseases include corneal neovascular disorders, such as corneal transplantation, herpetic keratitis, luetic keratitis, pterygium and neovascular pannus associated with contact lens use. Additional eye diseases also include age-related macular degeneration, presumed ocular histoplasmosis, retinopathy of prematurity and neovascular glaucoma.

In another aspect of the invention is the use of the formula (I) compounds in the inhibition of platelet aggregation and smooth muscle cell migration following vascular injury from percutaneous transluminal coronary angioplasty (PTCA). The instant compounds are useful in vascular remodeling.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention.

$C_{1-4}alkyl$  as applied herein is meant to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl.  $C_{1-6}alkyl$  additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any  $C_{1-4}alkyl$  or  $C_{1-6}alkyl$  group may be optionally substituted by  $R^7$  unless otherwise indicated.  $C_{0-4}alkyl$  and  $C_{0-6}alkyl$  additionally indicates that no alkyl group need be present (e.g., that a covalent bond is present).

C<sub>2</sub>-6alkenyl as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C<sub>2</sub>-6alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

5 Any C<sub>2</sub>-6alkenyl group may be optionally substituted by R<sup>7</sup> unless otherwise indicated.

C<sub>2</sub>-6alkynyl means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C<sub>2</sub>-6 alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne. Any sp<sup>3</sup> carbon atom in the C<sub>2</sub>-6alkynyl group may be optionally substituted by R<sup>7</sup>.

10 C<sub>1</sub>-4oxoalkyl refers to an alkyl group of up to four carbons wherein a CH<sub>2</sub> group is replaced by a C(O), or carbonyl, group. Substituted formyl, acetyl, 1-propanal, 2-propanone, 3-propanal, 2-butanone, 3-butanone, 1- and 4-butanal groups are representative. C<sub>1</sub>-6oxoalkyl includes additionally the higher analogues and isomers of five and six carbons substituted by a carbonyl group. C<sub>3</sub>-6oxoalkenyl and C<sub>3</sub>-6oxoalkynyl refers to a C<sub>3</sub>-6alkenyl or C<sub>3</sub>-6alkynyl group wherein a CH<sub>2</sub> group is replaced by C(O) group. C<sub>3</sub>-4oxoalkenyl includes 1-oxo-2-propenyl, 3-oxo-1-propenyl, 2-oxo-3-but enyl and the like.

15 20 A substituent on a C<sub>1</sub>-6 alkyl, C<sub>2</sub>-6 alkenyl, C<sub>2</sub>-6 alkynyl or C<sub>1</sub>-6 oxoalkyl group, such as R<sup>7</sup>, may be on any carbon atom which results in a stable structure, and is available by conventional synthetic techniques.

25 R<sup>14</sup>-C<sub>1</sub>-6 alkyl refers to a C<sub>1</sub>-6 alkyl group wherein in any position a carbon-hydrogen bond is replaced by a carbon-R<sup>14</sup> bond. R<sup>14</sup>-C<sub>2</sub>-6 alkenyl and R<sup>14</sup>-C<sub>2</sub>-6 alkynyl have a similar meaning with respect to C<sub>2</sub>-6 alkenyl and C<sub>2</sub>-6 alkynyl.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three moieties R<sup>7</sup>. In particular, R<sup>7</sup> may be C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkoxy, C<sub>1</sub>-4alkthio, trifluoroalkyl, OH, F, Cl, Br or I.

30 Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuran, benzimidazole, benzopyran, benzothiophene, furan, imidazole, indole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, 35 tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. A six membered ring heterocycle containing one or two nitrogens, such as piperidine, piperazine, tetrahydropyridine

and pyridine, are preferred heterocycles for the moiety Z. Any accessible combination of up to three substituents, such as chosen from R<sup>7</sup>, on the Het ring that is available by chemical synthesis and is stable is within the scope of this invention.

C<sub>3</sub>-7cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Typical of C<sub>3</sub>-7cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as chosen from R<sup>7</sup>, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention.

N as used herein indicates a nitrogen heterocycle, which may be a saturated or unsaturated stable five-, six- or seven-membered monocyclic ring, or a seven- to ten-membered bicyclic ring containing up to three nitrogen atoms or containing one nitrogen atom and a heteroatom chosen from oxygen and sulfur, and which may be substituted on any atom that results in a stable structure. The nitrogen atom in such ring may be substituted so as to result in a quaternary nitrogen. The nitrogen heterocycle may be substituted in any stable position by R<sup>20</sup>, for instance H, C<sub>1</sub>-<sub>4</sub>alkoxy, F, Cl, Br, I, NO<sub>2</sub>, NR'<sub>2</sub>, OH, CO<sub>2</sub>R', CONHR', CF<sub>3</sub>, R<sup>14</sup>-C<sub>0</sub>-<sub>4</sub>alkyl, R<sup>14</sup>-C<sub>1</sub>-<sub>4</sub>alkyl-S(O)<sub>u</sub> (e.g., where u is 0, 1 or 2) or C<sub>1</sub>-<sub>4</sub>alkyl substituted by any of the aforementioned substituents. Representative of N are pyrrolidine, pyrrolidine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, piperidine, piperazine, morpholine, pyridine, pyridinium, tetrahydropyridine, tetrahydro- and hexahydro-azepine, quinuclidine, quinuclidinium, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. In particular, N may be pyridyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, quinuclidinyl or tetrahydropyridinyl. N is preferably 4-pyridyl, 4-(2-amino-pyridyl), 4-tetrahydropyridyl, 4-piperidinyl or 4-piperazinyl.

When R<sup>b</sup> and R<sup>c</sup> are joined together to form a five- or six-membered aromatic or non-aromatic ring fused to the ring to which R<sup>b</sup> and R<sup>c</sup> are attached, the ring formed will generally be a five- or six-membered heterocycle selected from those listed above for Het, or will be a phenyl, cyclohexyl or cyclopentyl ring. Benzimidazolyl, 4-azabenzimidazolyl, 5-azabenzimidazolyl and substituted derivatives thereof are preferred moieties for W'.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the

benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bn refers to the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C<sub>1</sub>-alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. MeArg is N<sup>α</sup>-methyl arginine. Tet refers to 5-tetrazolyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethylamine, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBT refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DMF refers to dimethyl formamide, NBS refers to N-bromo-succinimide, Pd/C refers to a palladium on carbon catalyst, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, PPA refers to polyphosphoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

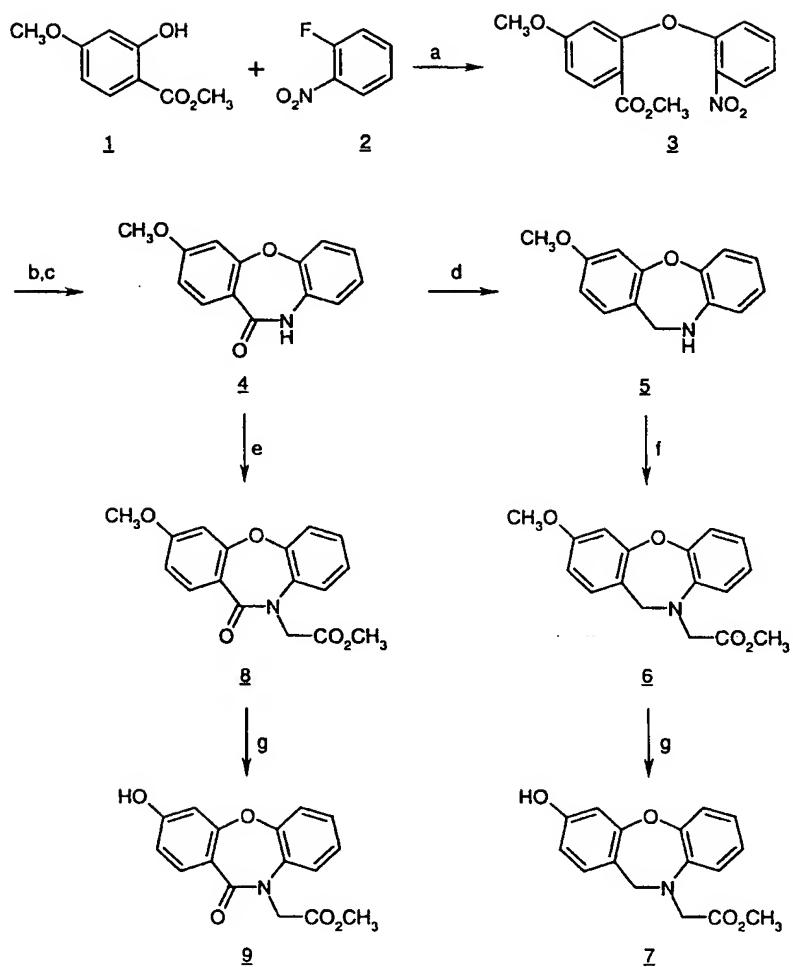
In certain cases, it may be desirable to further modify the group W or W' by appropriate reactions to introduce a functional group, or remove a protecting group, as further illustrated herein. The coupling will generally result in the formation of the U or V group, and methods for such coupling reactions are well known in the art.

WO 93/08174 (PCT/US92/08788; Genentech), WO 93/08174 (PCT/US92/08788; Genentech), WO 96/00730 (PCT/US95/08306; SmithKline Beecham), WO 96/00574 (PCT/US95/08146; SmithKline Beecham), WO 93/00095 (PCT/US92/05463; SmithKline Beecham) and WO 94/14776 (PCT/US93/12436; SmithKline Beecham) generally disclose such reactions and are incorporated herein by reference.

Compounds of formula (I) are prepared by methods analogous to those described in Schemes I-III and by methods analogous to those described in WO 97/01540 (PCT/US96/11108; SmithKline Beecham), the entire disclosure of which is incorporated herein by reference.

Compounds of the formula (I) wherein X<sup>2</sup> is O, X<sup>1</sup> is C(O) or CH<sub>2</sub> and m is 1 to 3 are prepared by methods analogous to those shown in Scheme I.

Scheme I



a)  $\text{K}_2\text{CO}_3$ , EtOH; b)  $\text{H}_2$ , 10% Pd/C, MeOH; c) toluene, reflux; d)  $\text{LiAlH}_4$ , THF;  
 5 e) i -  $\text{NaH}$ , DMF, ii - methyl bromoacetate; f) methyl bromoacetate,  $\text{Et}_3\text{N}$ , THF; g)  
 $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ .

Hydroxy esters, such as commercially available methyl 2-hydroxy-4-methoxybenzoate (**I-1**), is condensed with a fluoronitroarene, such as commercially available 2-fluoro-1-nitrobenzene (**I-2**), in the presence of a mild base, such as  $\text{K}_2\text{CO}_3$ , in a suitable solvent, such as EtOH, to give the di-aryl ether **I-3**. If necessary, the reaction may be heated to reflux to effect this condensation. The reduction of the nitro group is accomplished by hydrogenation over a suitable catalyst, such as 10% Pd/C, in a suitable solvent, such as MeOH. Many alternative

methods of reducing the nitro group exist and can be found in reference volumes such as Larcock, "Comprehensive Organic Transformations" (published by VCH Publishers).

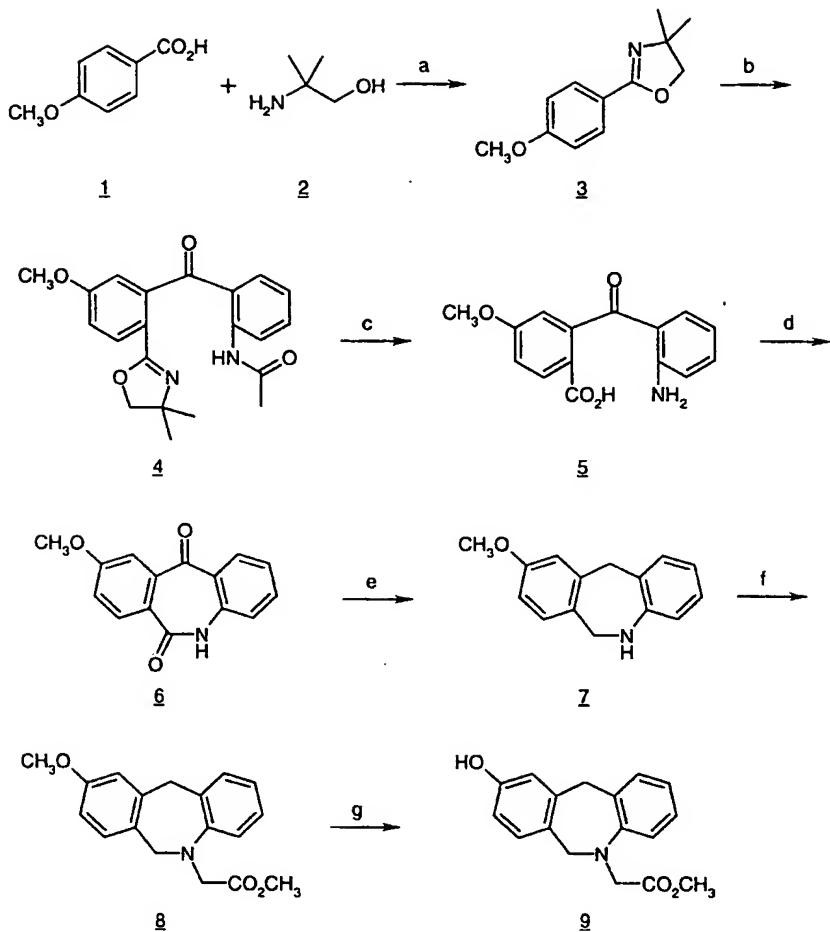
The resulting aminoester is heated in a suitable solvent, such as toluene, to 5 give the ring closed product **I-4**. Alternatively, the ester of **I-3** is first saponified with aqueous base, such as NaOH, in a polar solvent, such as MeOH. The resulting carboxylate is activated *in situ* by standard reagents, such as DCC, and allowed to react in an intramolecular fashion to give the cyclic amide, **I-4**.

Compound **I-4** is then deprotonated with a suitable base, such as NaH, in a 10 suitable solvent, such as DMF, and allowed to react with a suitable halo-ester, such as methyl bromoacetate to give **I-8**. Alternatively, the carbonyl group of **I-4** is reduced by standard methods, such as treating with lithium aluminum hydride in an aprotic polar solvent, such as THF. Many alternative methods of reducing the amide carbonyl group exist and can be found in reference volumes such as "Compendium 15 of Organic Synthetic Methods", Vol. I-VI (published by Wiley Interscience). The resulting amine **I-5** is reacted with a suitable halo-ester, such as methyl bromoacetate, in the presence of a mild base, such as triethylamine, in a polar solvent, such as THF, to give **I-6**.

The methyl ether of the tricyclic compounds, such as **I-6** or **I-8**, are 20 deprotected with a Lewis acid, such as BBr<sub>3</sub>, in a suitable solvent, such as CH<sub>2</sub>Cl<sub>2</sub> to give the corresponding phenols, such as **I-7** and **I-9**. Alternatively, the methyl ethers can be removed by treatment with AlCl<sub>3</sub> and a thiol, such as ethanethiol, in a suitable solvent, such as CH<sub>2</sub>Cl<sub>2</sub>. The resulting phenols, such as **I-7** or **I-9**, are then reacted according to the procedures found in WO 97/01540 (PCT/US96/11108; 25 SmithKline Beecham).

Compounds of formula (I) wherein X<sup>2</sup> is CH<sub>2</sub>, X<sup>1</sup> is CH<sub>2</sub> or C(O) and m is 1 to 3 are prepared by methods analogous to those described in Schemes II and III.

### Scheme II



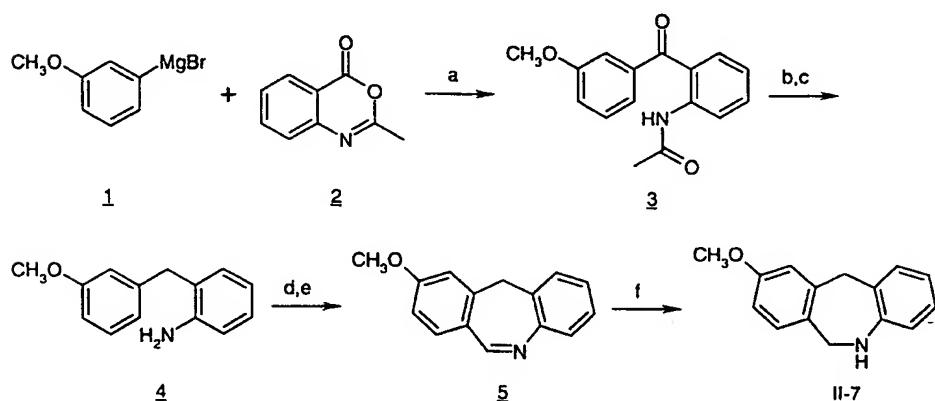
a) 2-amino-2-methyl-1-propanol; b) i- s-BuLi, Et<sub>2</sub>O; ii - 2-methyl-4H-3,1-benzoxazin-4-one; c) HCl; d) DCC; e) LiAlH<sub>4</sub>, THF; f) methyl bromoacetate, Et<sub>3</sub>N, THF; g) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>

A suitable aryl carboxylic acid, such as 4-methoxybenzoic acid, is reacted with a suitable aminoalcohol, such as 2-amino-2-methyl-1-propanol, according to the procedure of Meyers A I, et al. in *J. Org. Chem.* 1981, 46, 783 to give the resulting oxazoline II-3. Deprotonation of the aromatic ring ortho to the oxazoline is accomplished with a strong base, such as s-butyl lithium, in an aprotic polar solvent, such as Et<sub>2</sub>O. The resulting anion is the quenched with suitable electrophile, such as 2-methyl-4H-3,1-benzoxazin-4-one, to give the corresponding keto-amide II-4. Hydrolysis of the oxazoline and acetamide is accomplished by

treatment with a strong acid, such as aqueous hydrochloric acid, to give the amino acid **II-5**. The carboxylic acid of **II-5** is activated *in situ* by standard methods, such as DCC, and allowed to react in an intramolecular fashion to give the cyclic amide **II-6**. The ketone and carbonyl group of the amide are reduced simultaneously with a strong reducing agent, such as lithium aluminum hydride, in a suitable solvent, such as THF, to give the cyclic amine **II-7**. If necessary, the reaction can be heated to reflux to affect the transformation.

Scheme III

10



a) THF; b) Zn(Hg), HCl; c) HCl; d)  $\text{HCO}_2\text{H}$ ; e)  $\text{POCl}_3$ , PPA; f)  $\text{H}_2$ , 10% Pd/C, EtOH

15

Alternatively, **II-7** can be prepared by a process analogous to that shown in Scheme III. Treatment of **III-2** with a suitable organometallic reagent, such as 3-methoxyphenylmagnesium bromide, gives the corresponding ketoamide, such as **III-3**. Clemmensen reduction of the ketone using the general method of Dauben, *et al.* *J. Am. Chem. Soc.* **1954**, *76*, 3864, followed by hydrolysis of the acetamide with a strong acid, such as hydrochloric acid gives the amine **III-4**. Many alternative methods exist for reducing the ketone to the corresponding methylene compound and can be found in such reference volumes such as Larock, "Comprehensive Organic Transformations" (published by VCH publishers). The cyclization of **III-4** is accomplished by a Pictet-Spengler reaction. Thus, formylation of **III-4** with formic acid followed by an acid catalyzed cyclization with, for example, polyphosphoric acid, in  $\text{POCl}_3$  give the cyclic imine **III-5**. Standard methods, such as catalytic hydrogenation over Pd on carbon, are used to reduce the imine to the corresponding cyclic amine **II-7**.

The resulting amine **II-7** is reacted with a suitable halo-ester (Scheme II), such as methyl bromoacetate, in the presence of a mild base, such as triethylamine, in a polar solvent, such as THF, to give **II-8**. The methyl ether of **II-8** is demethylated with a Lewis acid, such as  $\text{BBr}_3$ , in a suitable solvent, such as 5  $\text{CH}_2\text{Cl}_2$ , to give the corresponding phenol, such as **II-9**. Alternatively, the methyl ethers can be removed by treatment with  $\text{AlCl}_3$  and a thiol, such as ethanethiol, in a suitable solvent, such as  $\text{CH}_2\text{Cl}_2$ . The resulting phenols, **II-9** is then reacted with the previously described Arg-VNR according to the procedures found in WO 10 97/01540 (PCT/US96/11108; SmithKline Beecham).

Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the 15 parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$  and  $\text{NH}_4^+$  are specific examples of cations present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises 20 a compound according to formula (I) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of 25 a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or 30 contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or 35 liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia,

agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glycetyl monostearate or glycetyl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds described herein which are antagonists of the vitronectin receptor, are useful for treating diseases wherein the underlying pathology is attributable to ligand or cell which interacts with the vitronectin receptor. For instance, these compounds are useful for the treatment of diseases wherein loss of the bone matrix creates pathology. Thus, the instant compounds are useful for the treatment of osteoporosis, hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastasis, bone loss due to immobilization or sex hormone deficiency. The compounds of this invention are also believed to have utility as antitumor, antiinflammatory, anti-angiogenic and anti-metastatic agents, and be useful in the treatment of cancer, atherosclerosis and restenosis. In particular, the compounds of this invention are useful for inhibiting restenosis following angioplasty.

The compounds of this invention which inhibit fibrinogen binding provide a method of inhibiting platelet aggregation and clot formation in a mammal, especially a human, which comprises the internal administration of a compound of formula (I) and a pharmaceutically acceptable carrier. Indications for such therapy include acute myocardial infarction (AMI), deep vein thrombosis, pulmonary embolism, dissecting aneurysm, transient ischemia attack (TIA), stroke and other infarct-related disorders, and unstable angina. Chronic or acute states of hyper-aggregability, such as disseminated intravascular coagulation (DIC), septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura (TTP), snake venom and immune diseases, are likely to be responsive to such treatment. In addition, the compounds of this invention may be useful in a

method for the prevention of metastatic conditions, the prevention or treatment of fungal or bacterial infection, inducing immunostimulation, treatment of sickle cell disease, and the prevention or treatment of diseases in which bone resorption is a factor.

5        This invention further provides a method for inhibiting the reocclusion of an artery or vein following fibrinolytic therapy, which comprises internal administration of a compound of formula (I) and a fibrinolytic agent. Administration of a compound of formula (I) in fibrinolytic therapy either prevents reocclusion completely or prolongs the time to reocclusion. When used in the  
10      context of this invention the term fibrinolytic agent is intended to mean any compound, whether a natural or synthetic product, which directly or indirectly causes the lysis of a fibrin clot. Plasminogen activators are a well known group of fibrinolytic agents. Useful plasminogen activators include, for example, anistreplase, urokinase (UK), pro-urokinase (pUK), streptokinase (SK), tissue  
15      plasminogen activator (tPA) and mutants, or variants, thereof.

The compounds of this invention may also be used *in vitro* to inhibit the aggregation of platelets in blood and blood products, *e.g.*, for storage, or for *ex vivo* manipulations such as in diagnostic or research use.

The compound is administered either orally or parenterally to the patient, in a  
20      manner such that the concentration of drug is sufficient to inhibit bone resorption, or inhibit platelet aggregation or other such indication. The pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy,  
25      parenteral administration is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times  
30      daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds may be tested in one of several biological assays to  
35      determine the concentration of compound which is required to have a given pharmacological effect.

### INHIBITION OF VITRONECTIN BINDING

*Solid-Phase [<sup>3</sup>H]-SK&F-107260 Binding to α<sub>v</sub>β<sub>3</sub>:* Human placenta or human platelet α<sub>v</sub>β<sub>3</sub> (0.1-0.3 mg/mL) in buffer T (containing 2 mM CaCl<sub>2</sub> and 1% octylglucoside) was diluted with buffer T containing 1 mM CaCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 5 1 mM MgCl<sub>2</sub> (buffer A) and 0.05% NaN<sub>3</sub>, and then immediately added to 96-well ELISA plates (Corning, New York, NY) at 0.1 mL per well. 0.1 - 0.2 µg of α<sub>v</sub>β<sub>3</sub> was added per well. The plates were incubated overnight at 4°C. At the time of the experiment, the wells were washed once with buffer A and were incubated with 10 0.1 mL of 3.5% bovine serum albumin in the same buffer for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed twice with 0.2 mL buffer A.

Compounds were dissolved in 100% DMSO to give a 2 mM stock solution, which was diluted with binding buffer (15 mM Tris-HCl (pH 7.4), 100 mM NaCl, 15 1 mM CaCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>) to a final compound concentration of 100 µM. This solution is then diluted to the required final compound concentration. Various concentrations of unlabeled antagonists (0.001 - 100 µM) were added to the wells in triplicates, followed by the addition of 5.0 nM of [<sup>3</sup>H]-SK&F-107260 (65 - 86 Ci/mmol).

The plates were incubated for 1 hr at room temperature. Following 20 incubation the wells were aspirated completely and washed once with 0.2 mL of ice cold buffer A in a well-to-well fashion. The receptors were solubilized with 0.1 mL of 1% SDS and the bound [<sup>3</sup>H]-SK&F-107260 was determined by liquid scintillation counting with the addition of 3 mL Ready Safe in a Beckman LS Liquid Scintillation Counter, with 40% efficiency. Nonspecific binding of [<sup>3</sup>H]-SK&F- 25 107260 was determined in the presence of 2 µM SK&F-107260 and was consistently less than 1% of total radioligand input. The IC<sub>50</sub> (concentration of the antagonist to inhibit 50% binding of [<sup>3</sup>H]-SK&F-107260) was determined by a nonlinear, least squares curve-fitting routine, which was modified from the LUNDON-2 program. The K<sub>i</sub> (dissociation constant of the antagonist) was calculated according to the 30 equation: K<sub>i</sub> = IC<sub>50</sub>/(1 + L/K<sub>d</sub>), where L and K<sub>d</sub> were the concentration and the dissociation constant of [<sup>3</sup>H]-SK&F-107260, respectively.

Compounds of the present invention inhibit vitronectin binding to SK&F 107260 in the concentration of about 0.1 micromolar.

Compounds of this invention are also tested for *in vitro* and *in vivo* bone 35 resorption in assays standard in the art for evaluating inhibition of bone formation, such as the pit formation assay disclosed in EP 528 587, which may also be

performed using human osteoclasts in place of rat osteoclasts, and the ovariectomized rat model, described by Wronski *et al.*, *Cells and Materials* 1991, Sup. 1, 69-74.

#### **PARATHYROIDECTOMIZED RAT MODEL**

5 Each experimental group consists of 5-6 male Sprague-Dawley rats. The rats are parathyroidectomized (by the vendor, Taconic Farms) 7 days prior to use. Twenty four hours prior to use, circulating ionized calcium levels are measured in whole blood immediately after it has been withdrawn by tail venipuncture into heparinized tubes. Rats are included if ionized Ca level (measured with a Ciba-Corning model 634 calcium pH 10 analyzer) is •1.2 mM/L. The rats are then put on a diet of calcium-free chow and deionized water. At the start of the experiment the rats weigh approximately 100g. Baseline Ca levels are measured and the rats are administered control vehicle (saline) or compound (dissolved in saline) as a single intravenous (tail vein) bolus injection followed immediately by a single subcutaneous injection of either human parathyroid hormone 1-15 34 peptide (hPTH1-34, dose 0.2mg/kg in saline/0.1% bovine serum albumen, Bachem, Ca) or the PTH vehicle. The calcemic response to PTH (and any effect of compound on this response) is measured 2h after compound/PTH administration.

#### **RAT ULNA DRIFT MODEL**

20 Each experimental group consists of 8-10 male Sprague-Dawley or Wistar rats of approximately 30-40g body weight at the start of the experiment. The agent being tested is administered by an appropriate route as single or multiple daily doses for a period of seven days. Prior to administration of the first dose, the rats are given a single dose of a fluorescent marker (tetracycline 25mg/kg, or calcein 10mg/kg) that labels the position of 25 bone forming surfaces at that point in time. After dosing of compound has been completed, the rats are killed and both forelimbs are removed at the elbow, the foot is removed at the ankle and the skin removed. The sample is frozen and mounted vertically on a microtome chuck. Cross sections of the midshaft region of the ulna are cut in the cryostat. The rate of bone resorption is measured morphometrically in the medial-dorsal 30 portion of the cortical bone. The measurement is done as follows: the amount of bone resorbed at the periosteal surface is equal to the distance by which the periosteal surface has advanced towards the fluorescent label which had been incorporated at the endosteal bone formation surface on day zero; this distance is calculated by subtracting the width of bone between the label and the periosteal surface on day 7 from the width on day zero; the 35 resorption rate in microns per day is calculated by dividing the result by 7.

**HUMAN OSTEOCLAST RESORPTION ASSAY ("PIT ASSAY")**

- Aliquots of osteoclastoma-derived cell suspensions are removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000rpm, 5 mins at 4°C).
- 5   • Aspirate the medium and replace it with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium. Incubate for 30 mins on ice and mix the cell suspension frequently.
- The cells are washed x2 with cold RPMI-1640 by centrifugation (1000rpm, 5 mins at 4°C) and the cells are transferred to a sterile 15 ml centrifuge tube. The number of mononuclear cells are enumerated in an improved Neubauer counting chamber.
- 10   • Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, are removed from their stock bottle and placed into 5 ml of fresh medium (this washes away the toxic azide preservative). The medium is removed by immobilizing the beads on a magnet and is replaced with fresh medium.
- 15   • The beads are mixed with the cells and the suspension is incubated for 30 mins on ice. The suspension is mixed frequently.
  - The bead-coated cells are immobilized on a magnet and the remaining cells (osteoclast-rich fraction) are decanted into a sterile 50 ml centrifuge tube.
  - Fresh medium is added to the bead-coated cells to dislodge any trapped osteoclasts.
- 20   • This wash process is repeated x10. The bead-coated cells are discarded.
  - The osteoclasts are enumerated in a counting chamber, using a large-bore disposable plastic pasteur to charge the chamber with the sample.
  - The cells are pelleted by centrifugation and the density of osteoclasts adjusted to  $1.5 \times 10^4/\text{ml}$  in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate.
- 25   • 3ml aliquots of the cell suspension ( per treatment) are decanted into 15ml centrifuge tubes. The cells are pelleted by centrifugation.
  - To each tube 3ml of the appropriate treatment are added (diluted to 50 uM in the EMEM medium). Also included are appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/ml) and an isotype control (IgG2a diluted to 100 ug/ml). Incubate at 37°C for 30 mins.
  - 0.5ml aliquots of the cells are seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 hours. Each treatment is screened in quadruplicate.
  - The slices are washed in six changes of warm PBS (10 ml / well in a 6-well plate) and then placed into fresh treatment or control. Incubate at 37°C for 48 hours.
- 30
- 35

**tartrate resistant acid phosphatase (trap) procedure** (selective stain for cells of the osteoclast lineage).

- The slices are washed in phosphate buffered saline and fixed in 2% gluteraldehyde (in 0.2M sodium cacodylate) for 5 mins.
- 5 • They are washed in water and incubated in TRAP buffer for 5 mins at 37°C.
- Following a wash in cold water they are incubated in cold acetate buffer / fast red garnet for 5 mins at 4°C.
- Excess buffer is aspirated, and the slices are air dried following a wash in water.
- The TRAP positive osteoclasts are enumerated by bright-field microscopy and are 10 then removed from the surface of the dentine by sonication.
- Pit volumes are determined using the Nikon/Lasertec ILM21W confocal microscope.

#### INHIBITION OF RGD-MEDIATED $\alpha_{IIb}\beta_3$ BINDING

##### 15 *Purification of $\alpha_{IIb}\beta_3$*

Ten units of outdated, washed human platelets (obtained from Red Cross) were lysed by gentle stirring in 3% octylglucoside, 20 mM Tris-HCl, pH 7.4, 140 mM NaCl, 2 mM CaCl<sub>2</sub> at 4°C for 2 h. The lysate was centrifuged at 100,000g for 1 h. The supernatant obtained was applied to a 5 mL lentil lectin sepharose 4B 20 column (E.Y. Labs) pre-equilibrated with 20 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl<sub>2</sub>, 1% octylglucoside (buffer A). After 2 h incubation, the column was washed with 50 mL cold buffer A. The lectin-retained  $\alpha_{IIb}\beta_3$  was eluted with buffer A containing 10% dextrose. All procedures were performed at 4°C. The  $\alpha_{IIb}\beta_3$  obtained was >95% pure as shown by SDS polyacrylamide gel electrophoresis.

25

##### *Incorporation of $\alpha_{IIb}\beta_3$ in Liposomes*

A mixture of phosphatidylserine (70%) and phosphatidylcholine (30%) (Avanti Polar Lipids) were dried to the walls of a glass tube under a stream of nitrogen. Purified  $\alpha_{IIb}\beta_3$  was diluted to a final concentration of 0.5 mg/mL and 30 mixed with the phospholipids in a protein:phospholipid ratio of 1:3 (w:w). The mixture was resuspended and sonicated in a bath sonicator for 5 min. The mixture was then dialyzed overnight using 12,000-14,000 molecular weight cutoff dialysis tubing against a 1000-fold excess of 50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl<sub>2</sub> (with 2 changes). The  $\alpha_{IIb}\beta_3$ -containing liposomes were centrifuged at 35 12,000g for 15 min and resuspended in the dialysis buffer at a final protein concentration of approximately 1 mg/mL. The liposomes were stored at -70°C until needed.

**Competitive Binding to  $\alpha_{IIb}\beta_3$** 

The binding to the fibrinogen receptor ( $\alpha_{IIb}\beta_3$ ) was assayed by an indirect competitive binding method using [<sup>3</sup>H]-SK&F-107260 as an RGD-type ligand. The 5 binding assay was performed in a 96-well filtration plate assembly (Millipore Corporation, Bedford, MA) using 0.22  $\mu$ m hydrophilic durapore membranes. The wells were precoated with 0.2 mL of 10  $\mu$ g/mL polylysine (Sigma Chemical Co., St. Louis, MO.) at room temperature for 1 h to block nonspecific binding. Various concentrations of unlabeled benzadiazapines were added to the wells in 10 quadruplicate. [<sup>3</sup>H]-SK&F-107260 was applied to each well at a final concentration of 4.5 nM, followed by the addition of 1  $\mu$ g of the purified platelet  $\alpha_{IIb}\beta_3$ -containing liposomes. The mixtures were incubated for 1 h at room temperature. The  $\alpha_{IIb}\beta_3$ -bound [<sup>3</sup>H]-SK&F-107260 was separated from the unbound by filtration using a Millipore filtration manifold, followed by washing with ice-cold buffer (2 times, 15 each 0.2 mL). Bound radioactivity remaining on the filters was counted in 1.5 mL Ready Solve (Beckman Instruments, Fullerton, CA) in a Beckman Liquid Scintillation Counter (Model LS6800), with 40% efficiency. Nonspecific binding was determined in the presence of 2  $\mu$ M unlabeled SK&F-107260 and was consistently less than 0.14% of the total radioactivity added to the samples. All data 20 points are the mean of quadruplicate determinations.

Competition binding data were analyzed by a nonlinear least-squares curve fitting procedure. This method provides the IC<sub>50</sub> of the antagonists (concentration of the antagonist which inhibits specific binding of [<sup>3</sup>H]-SK&F-107260 by 50% at equilibrium). The IC<sub>50</sub> is related to the equilibrium dissociation constant (K<sub>i</sub>) of the 25 antagonist based on the Cheng and Prusoff equation: K<sub>i</sub> = IC<sub>50</sub>/(1+L/K<sub>d</sub>), where L is the concentration of [<sup>3</sup>H]-SK&F-107260 used in the competitive binding assay (4.5 nM), and K<sub>d</sub> is the dissociation constant of [<sup>3</sup>H]-SK&F-107260 which is 4.5 nM as determined by Scatchard analysis.

Inhibition of platelet aggregation may be measured by the method described 30 in WO 93/00095 (PCT/US/92/05463). *In vivo* thrombus formation is demonstrated by recording the systemic and hemodynamic effects of infusion of the peptides into anesthetized dogs according to the methods described in Aiken et al., *Prostaglandins*, 19, 620 (1980).

**35 Vascular smooth muscle cell migration assay**

The compounds of the instant invention were tested for their ability to inhibit the migration and proliferation of smooth muscle tissue in an artery or vein in order

to assess their ability to prevent restenosis of an artery, such as that which typically occurs following angioplasty.

Rat or human aortic smooth muscle cells were used. The cell migration was monitored in a Transwell cell culture chamber by using a polycarbonate membrane with pores of 8 um (Costar). The lower surface of the filter was coated with vitronectin. Cells were suspended in DMEM supplemented with 0.2% bovine serum albumin at a concentration of 2.5 - 5.0 x 10<sup>6</sup> cells/mL, and were pretreated with test compound at various concentrations for 20 min at 20°C. The solvent alone was used as control. 0.2 mL of the cell suspension was placed in the upper compartment of the chamber. The lower compartment contained 0.6 mL of DMEM supplemented with 0.2% bovine serum albumin. Incubation was carried out at 37°C in an atmosphere of 95% air/5% CO<sub>2</sub> for 24 hr. After incubation, the non-migrated cells on the upper surface of the filter were removed by gentle scraping. The filter was then fixed in methanol and stained with 10% Giemsa stain. Migration was measured either by a) counting the number of cells that had migrated to the lower surface of the filter or by b) extracting the stained cells with 10% acetic acid followed by determining the absorbance at 600 nM.

#### Examples

20

Nuclear magnetic resonance spectra were obtained using either a Bruker AM 250 or Bruker AC 400 spectrometer. Chemical shifts are reported in parts per million ( $\delta$ ) downfield from the internal standard tetramethylsilane. Mass spectra were taken on either VG 70 FE or VG ZAB HF instruments using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, New Jersey.

25

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical and preparative HPLC were carried out on Bechman Chromatographs. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada.

Example 1Preparation of 3-[3-(2-pyridylamino)propyloxy]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-10-acetic acid

5

a) Methyl 4-methoxy-2-(*o*-nitrophenoxy)-benzoate

2-Fluoronitrobenzene (6.00 mL, 56.9 mmol) and potassium carbonate (30.5 g., 22.1 mmol) were added to methyl 2-hydroxy-4-methoxybenzoate (10.1 g., 55.6 mmol) in DMF (100 mL). The reaction was heated in an oil bath at 110 °C. After 10 20 h, the reaction was diluted with water and extracted with ethyl acetate (3x). The organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under vacuum to give a dark residue. Flash chromatography (20% EtOAc/hexanes, silica gel) gave 16.1 g of the desired product as a yellow solid. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.95-8.05 (m, 2H), 7.40-7.50 (m, 1H), 7.10-7.17 (m, 1H), 6.75-6.85 (m, 15 2H), 6.63 (t, 1H), 3.85 (s, 3H), 3.70

b) Methyl 4-methoxy-2-(*o*-aminophenoxy)-benzoate

A reaction vessel was charged with methyl 4-methoxy-2-(*o*-nitrophenoxy)-benzoate (16.1 g, 53.1 mmol) and 10% Pd/C (100 mg) in MeOH (100 mL). The 20 reaction vessel was flushed with hydrogen and then fitted with a hydrogen filled balloon. After 24 hours, the reaction was filtered through celite and the residue was evaporated under vacuum to yield 14.3 g of the desired product. MS (ES+) m/z 274.2 (M+H)<sup>+</sup>

25 c) 3-Methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine-11-one

To methyl 4-methoxy-2-(*o*-aminophenoxy)-benzoate (14.3 g, 52.3 mmol) in toluene (500 mL) was added 1N NaOH (150 mL, 150 mmol). The reaction was heated to 70 °C for 3 days. The solvent was removed under reduced pressure and the product was isolated by flash chromatography (EtOAc, silica gel) to give 9.85 g 30 of the desired product. MS (ES+) m/z 242.2 (M+H<sup>+</sup>).

## d) 3-Methoxy-10,11-dihydrodibenzo[b,f][1,4]-oxazepine

To 3-methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine-11-one (9.84 g, 40.9 mmol) in THF (150 mL) at RT was added LiAlH<sub>4</sub> (30 mL, 1.0 M in THF, 30 mmol). After 18 h, the reaction was diluted with toluene and cooled to 0 °C. The reaction was quenched by adding water (1.6 mL.) and NaF (5.0 g.) and stirring vigorously for 1 h. The resulting precipitate was removed by filtration and the

eluent was concentrated under vacuum to give the crude product. Flash chromatography ( $\text{CHCl}_3$ , silica gel) gave 6.28 g of the desired material as a pale yellow solid.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ).  $\delta$  6.50-7.15(m, 7H), 4.42 (s, 2H), 3.78 (s, 3H), 3.28 (br. s., 1H).

5

e) Methyl 3-methoxy-10,11-Dihydrodibenzo[b,f][1,4]-oxazepine-10-acetate  
3-Methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine (0.43 g, 1.90 mmol) was dissolved in THF (5 mL). Methyl bromoacetate (0.25 mL, 2.64 mmol.) was added followed by triethylamine (0.25 mL, 1.80 mmol). After 24 h at reflux, the solvent was removed under vacuum and the residue was adsorbed onto silica gel. Flash chromatography ( $\text{CHCl}_3$  to 10% MeOH/ $\text{CHCl}_3$ , silica gel) gave 0.40 g of the desired material. MS(ES+) m/z 300.2 ( $\text{M}+\text{H}^+$ ).

10

f) Methyl 3-hydroxy-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-10-acetate  
Methyl 3-methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine-acetate (0.40 g, 1.34 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was treated with  $\text{BBr}_3$  (6.70 mL, 1.0 M in  $\text{CH}_2\text{Cl}_2$ , 6.70 mmol). After 20 minutes, the reaction was quenched with methanol and the solvent was removed under vacuum. Flash chromatography ( $\text{CHCl}_3$ , silica gel) gave 0.25 g of the desired material. MS (ES+) m/z 286.3 ( $\text{M}+\text{H}^+$ ).

15

g) Methyl 3-[3-(*N*-*t*-butoxycarbonyl-2-aminopyridyl)propyloxy]-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-10-acetate-*N*-oxide  
To *N*-(*t*-butoxycarbonyl)-3-(2-aminopyridyl)-propanol (0.49 g, 1.81 mmol) in pyridine (5 mL) at 0 °C was added mesyl chloride (0.18 mL, 2.26 mmol). After 1 h at 0 °C, the reaction was extracted with EtOAc. The combined organic extracts were washed with 1N HCl, 1N, NaHCO<sub>3</sub> and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the crude mesylate was used without further purification in the next step.

20

To the methyl-3-hydroxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine-1-acetate (0.25 g, 0.88 mmol) in DMSO (15 mL) was added NaH (27 mg, 60% dispersion in oil, 0.68 mmol). After the bubbling stopped, the crude mesylate (obtained above) was added and the reaction was allowed to proceed at RT. After 20 h, the solvent was removed under reduced pressure and the product isolated by flash chromatography (EtOAc, silica gel) to give 0.19 g of the desired product.

25

h) Methyl 3-[3-(2-aminopyridyl)propyloxy]-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-10-acetate

Methyl 3-[3-(*N*-*t*-butoxycarbonyl-2-aminopyridyl)propyloxy]-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-10-acetate-*N*-oxide (0.19 g, 0.36 mmol) was  
5 treated with 4 N HCl/dioxane (5 mL) at RT. After 1 h, the solvent was removed under vacuum and the residue was azeotroped with toluene (2x). This material was redissolved in ethanol (5 mL) and triethylamine (0.10 mL, 0.72 mmol), cyclohexene (0.50 mL, 4.90 mmol) and 10% Pd/C were added. The reaction was heated to reflux for 20 h. After allowing the reaction to cool to RT, the catalyst was removed by  
10 filtration through celite and the filtrate was concentrated under vacuum to give 0.17 g of the desired material. This was used without further purification. MS (ES+) m/z 420.2 (M+H<sup>+</sup>).

i) 3-[3-(2-Pyridylamino)propyloxy]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-10-acetic acid

To methyl 3-[3-(2-aminopyridyl)propyloxy]-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-10-acetate (0.17 g, 0.42 mmol) in MeOH (2 mL) was added 1N NaOH (2 mL). The reaction was heated to 55 °C for 20 h. The reaction was allowed to cool to RT and then neutralized with 1N HCl. Cooling the solution to 0 °C resulted in the  
20 product forming as a precipitate. This was collected and dried under vacuum to give 17 mg of the desired material as a white solid. MS(ES+) m/z 406.1 (M+H<sup>+</sup>). Anal. (C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>·0.75HCl) calcd: C, 63.83; H, 5.53; N, 9.71. Found: C, 63.67; H, 5.27; N, 9.49.

25

## Example 2

### Oral Dosage Unit Composition

A tablet for oral administration is prepared by mixing and granulating 20 mg  
30 of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

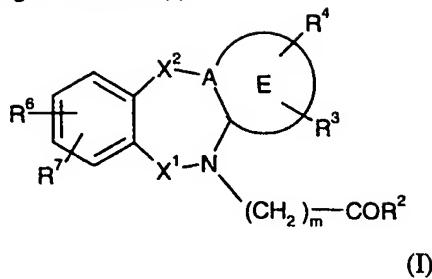
The above description fully discloses how to make and use the present  
35 invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and

other publications which are cited herein comprises the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I):

5



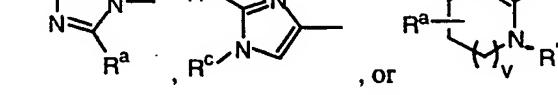
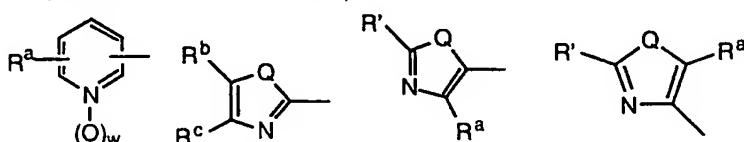
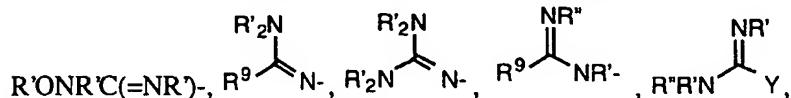
wherein:

- A is C or N;
- E is a five- or six-membered heteroaromatic or heterocyclic ring, or a six-membered aromatic ring;
- X<sup>1</sup> is CHR<sup>1</sup>, C(O) or C(S);
- X<sup>2</sup> is CR<sup>5</sup>R<sup>5</sup>, NR<sup>5</sup>, S(O)<sub>u</sub> or O;
- R<sup>1</sup> is H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;
- R<sup>2</sup> is -OR', -NR'R'', -NR'SO<sub>2</sub>R'', -NR'OR', -OCR'<sub>2</sub>C(O)OR', -OCR'<sub>2</sub>OC(O)-R';
- R', -OCR'<sub>2</sub>C(O)NR'<sub>2</sub>, CF<sub>3</sub> or -COCR'<sub>2</sub>R<sup>2</sup>;
- R<sup>2</sup>' is -OR', -CN, -S(O)<sub>r</sub>R', S(O)<sub>2</sub>NR'<sub>2</sub>, -C(O)R'C(O)NR'<sub>2</sub> or -CO<sub>2</sub>R';
- R' is H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;
- R'' is R', -C(O)R' or -C(O)OR<sup>5</sup>;
- R''' is C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;
- R<sup>5</sup> and R<sup>5</sup>' are independently H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;
- R<sup>6</sup> is W-(CR'<sub>2</sub>)<sub>q</sub>-Z-(CR'R<sup>10</sup>)<sub>r</sub>-U-(CR'<sub>2</sub>)<sub>s</sub>-V- or W'-(CR'<sub>2</sub>)<sub>q</sub>-U-(CR'<sub>2</sub>)<sub>s</sub>-;
- R<sup>3</sup>, R<sup>4</sup> and R<sup>7</sup> are independently H, halo, -OR<sup>12</sup>, -SR<sup>12</sup>, -CN, -NR'R<sup>12</sup>, -NO<sub>2</sub>, -CF<sub>3</sub>, CF<sub>3</sub>S(O)<sub>r</sub>, -CO<sub>2</sub>R', -CONR'<sub>2</sub>, R<sup>14</sup>-C<sub>0-6</sub>alkyl-, R<sup>14</sup>-C<sub>1-6</sub>oxoalkyl-, R<sup>14</sup>-C<sub>2-6</sub>alkenyl-, R<sup>14</sup>-C<sub>2-6</sub>alkynyl-, R<sup>14</sup>-C<sub>0-6</sub>alkyloxy-, R<sup>14</sup>-C<sub>0-6</sub>alkylamino- or R<sup>14</sup>-C<sub>0-6</sub>alkyl-S(O)<sub>r</sub>;
- R<sup>8</sup> is R', C(O)R', CN, NO<sub>2</sub>, SO<sub>2</sub>R' or C(O)OR<sup>5</sup>;
- R<sup>9</sup> is R', -CF<sub>3</sub>, -SR', or -OR';
- R<sup>10</sup> is H, C<sub>1-4</sub>alkyl or -NR'R'';
- R<sup>12</sup> is R', -C(O)R', -C(O)NR'<sub>2</sub>, -C(O)OR<sup>5</sup>, -S(O)<sub>m</sub>R' or S(O)<sub>2</sub>NR'<sub>2</sub>;
- R<sup>14</sup> is H, C<sub>3-6</sub>cycloalkyl, Het or Ar;
- R<sup>15</sup> is H, C<sub>1-10</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-8</sub>alkyl or Ar-C<sub>0-8</sub>alkyl;

U and V are absent or CO, CR'2, C(=CR'<sup>15</sup>)<sub>2</sub>, S(O)<sub>n</sub>, O, NR<sup>15</sup>, CR<sup>15</sup>'OR<sup>15</sup>, CR'(OR")CR'<sub>2</sub>, CR'<sub>2</sub>CR'(OR"), C(O)CR'<sub>2</sub>, CR'<sup>15</sup><sub>2</sub>C(O), CONR<sup>15</sup>, NR<sup>15</sup>CO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR<sup>15</sup>, NR<sup>15</sup>C(S), SO<sub>2</sub>NR<sup>15</sup>, NR<sup>15</sup>SO<sub>2</sub>, N=N, NR<sup>15</sup>NR<sup>15</sup>, NR<sup>15</sup>CR'<sub>2</sub>, NR<sup>15</sup>CR'<sup>15</sup><sub>2</sub>, CR'<sup>15</sup><sub>2</sub>O, OCR'<sub>2</sub>, C≡C, CR<sup>15</sup>=CR'<sub>15</sub>, Het, or Ar, provided

5 that U and V are not simultaneously absent;

W is R'R"N-, R'R"NRN-, R'R"NRNCO-, R'<sub>2</sub>NRNC(=NR')-,



, or



10

Q is NR', O or S;

R<sup>a</sup> is H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl, halogen, OR<sup>1</sup>, SR<sup>1</sup>, COR<sup>1</sup>, OH, NO<sub>2</sub>, N(R<sup>1</sup>)<sub>2</sub>, CO(NR<sup>1</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>,

15 R<sup>b</sup> and R<sup>c</sup> are independently selected from H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl, halogen, OR<sup>1</sup>, SR<sup>1</sup>, COR<sup>1</sup>, OH, NO<sub>2</sub>, N(R<sup>1</sup>)<sub>2</sub>, CO(NR<sup>1</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, or R<sub>b</sub> and R<sub>c</sub> are joined together to form a five or six membered aromatic or non-aromatic ring, optionally substituted by halogen, C<sub>1-4</sub>alkyl, OR<sup>1</sup>, SR<sup>1</sup>, COR<sup>1</sup>, OH, NO<sub>2</sub>, N(R<sup>1</sup>)<sub>2</sub>, CO(NR<sup>1</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, CN, or R'RNC(=NR')-;

20 X is N=CR', C(O) or O;

Y is absent, S or O;

Z is (CH<sub>2</sub>)<sub>t</sub>, Het, Ar or C<sub>3-7</sub>cycloalkyl;

m is 1 or 2;

n is 0, 1, 2 or 3;

25 q is 0, 1, 2 or 3;

r is 0, 1 or 2;

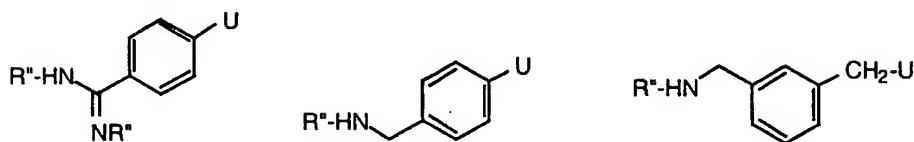
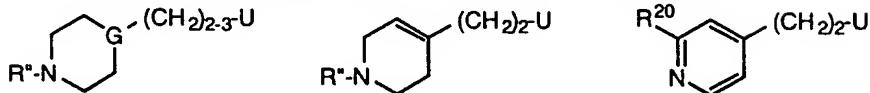
s is 0, 1 or 2;

t is 0, 1 or 2;

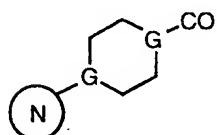
u is 0, 1 or 2;  
 v is 0, 1 or 2; and  
 w is 0 or 1; or  
 a pharmaceutically acceptable salt thereof.

5

2. A compound according to claim 1 wherein R<sup>6</sup> is chosen from:



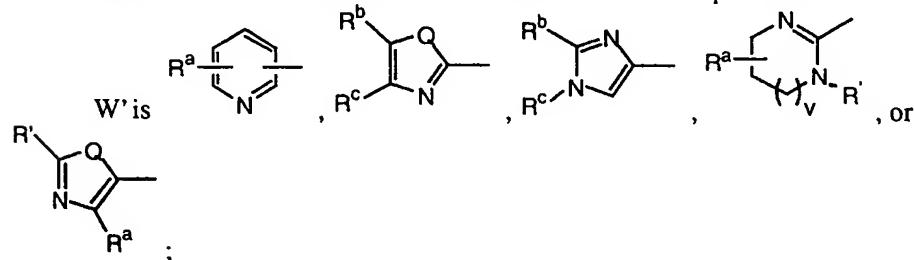
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, R''HNC(=NH)NH-(CH<sub>2</sub>)<sub>3</sub>(CHR<sup>10</sup>)-U, and R''HN-(CH<sub>2</sub>)<sub>5</sub>-U  
 wherein G is N or CH, R<sup>20</sup> is hydrogen, amino, mono or di-C<sub>1-4</sub>alkylamino,  
 hydroxy or C<sub>1-4</sub>alkyl, and U is NR'CO, CONR', (CH<sub>2</sub>)CO, CH=CH, C≡C, CH<sub>2</sub>O,  
 OCH<sub>2</sub> and (CH<sub>2</sub>)<sub>2</sub>.

15

3. A compound according to claim 1 wherein R<sup>6</sup> is W'-(CR'<sub>2</sub>)<sub>q</sub>-U-, and



Q is NH;

20

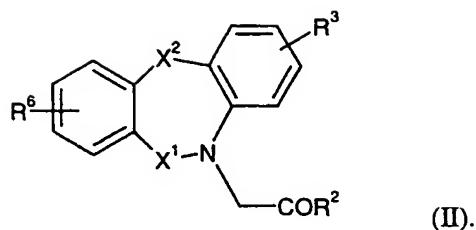
R' is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, halogen or RNH.

R<sup>b</sup> and R<sup>c</sup> are joined to form an optionally substituted cyclohexyl, phenyl or pyridyl ring, and

U- is (CH<sub>2</sub>)<sub>q</sub>-NR'CO, (CH<sub>2</sub>)<sub>q</sub>-CH<sub>2</sub>O or (CH<sub>2</sub>)<sub>q</sub>-CH<sub>2</sub>CH<sub>2</sub>.

25

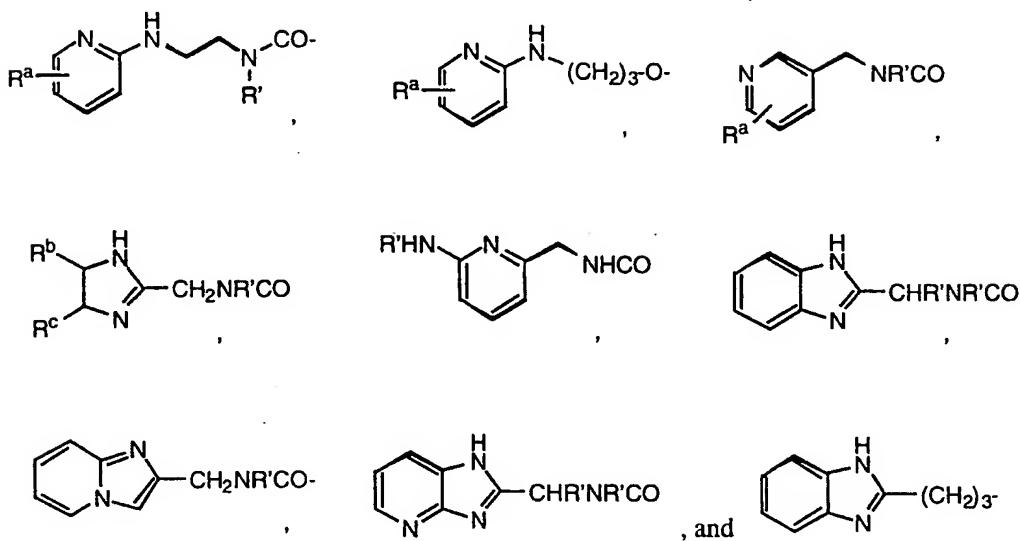
4. A compound according to claim 1 which is:



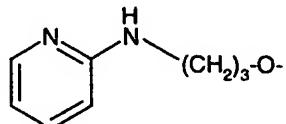
5. A compound according to claim 4 wherein  $X^1$  is  $\text{CH}_2$  and  $X^2$  is O.

5 6. A compound according to claim 4 wherein  $R^2$  is -OH.

7. A compound according to claim 4 wherein  $R^6$  is



10 8. A compound according to claim 4 wherein  $R^6$  is



15 9. A compound according to claim 1 which is 3-[3-(2-pyridyl)aminopropoxy]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-10-acetic acid or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to any one of claims 1-9 and a pharmaceutically acceptable carrier.
11. A method of inhibiting the fibrinogen receptor comprising administering a compound according to claim 1.
12. A method of inhibiting a vitronectin receptor comprising administering a compound according to claim 1.
- 10 13. A method of for treating osteoporosis, atherosclerosis, cancer or restenosis following angioplasty in a mammal comprising administering a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 15 14. A method of treating stroke, transient ischemia attacks, myocardial infarction or inhibiting reocclusion following thrombolytic therapy comprising administering a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 15 15. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament.
- 20 16. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of the fibrinogen receptor in a mammal in need thereof.
- 25 17. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of the vitronectin receptor in a mammal in need thereof.
- 30 18. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of osteoporosis, atherosclerosis, cancer or restenosis following angioplasty.
- 35 19. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of stroke, transient ischemia attacks, myocardial infarction or for the inhibition of reocclusion following thrombolytic therapy.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/18379

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 223/20; A61K 31/55  
 US CL :514/217; 540/522, 586

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/217; 540/522, 586

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,512,563 A (ALBRIGHT et al.) 30 April 1996, entire columns 2-9.	1-4, 6-8, 10-19
A	US 4,551,451 A (PESTELLINI et al.) 05 November 1985, entire columns 1 and 2.	1-4, 6-8, 10-19
A	US 3,905,977 A (SIMON et al.) 16 September 1975, entire columns 1 and 2	1-4, 6-8, 10-19

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 NOVEMBER 1998

Date of mailing of the international search report

22 DEC 1998

Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US98/18379

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-4, 6-8, 10-19

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US98/18379

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-4, 6-8, 10-19, drawn to compounds where A is C, X<sup>1</sup> is C and X<sup>2</sup> is C.

Group II, claim(s) 1-4, 6-8, 10-19, drawn to compound where A is C, X<sup>1</sup> is C and X<sup>2</sup> is N.

Group III, claims 1-19, drawn to compound where A is C, X<sup>1</sup> is C and X<sup>2</sup> is O or S .

Group IV, claim(s)1-4, 6-8, 10-19, drawn to compound where A is N, X<sup>1</sup> is C and X<sup>2</sup> is C, O or S.

Group V, claim(s) 1-4, 6-8, 10-19, drawn to compound where A is N, X<sup>1</sup> is C and X<sup>2</sup> is N.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions of Groups I-V are drawn to structurally dissimilar compounds. They are made and used independently one does not require the other for their use. If, say, the tricyclic azepines of Group I, were anticipated, applicants would not acquiesce in the objection of any of the Groups II-V there over or vice-versa and, thus, they are not linked to the same or corresponding special technical features.